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Synthesis of 1,2,4-trisubstituted-1,2,5,6-tetrahydropyridines

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ABSTRACT

A novel method for the synthesis of 1,2,4-trisubstituted- or 1,2,3,4-tetrasubstituted-1,2,5,6-tetrahydropyridine is presented. The process was carried out by the bromomethoxylation of 4-substituted-1,2,5,6-tetrahydropyridines **1** with *N*-bromosuccinimide (NBS) in methanol, dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and boron trifluoride etherate (BF_3-OEt_2)-catalyzed cross coupling of the corresponding enamine with trimethylsilyl-based nucleophiles. Homokainoid analogs were also synthesized via the protocol.

1. Introduction

Functionalized piperidines are prevalent scaffolds that serve as crucial building blocks for numerous syntheses of natural products and nitrogen heterocycles and have been previously reviewed.[1] The syntheses of these types of compounds have been studied extensively as the development of new drugs containing six-membered ring heterocycles becomes more and more common.[2] It is necessary to develop new routes for this class of compounds. The substituted pipecolic acid or a related derivative (e.g., α-amino nitrile) is a key ingredient in many therapeutic agents with piperidinyl substituent, as an important bioactive component in pharmaceutical research.[3] For example, 4-methylpipecolic acid is a constituent of argatroban (MD-805), a potent inhibitor of the enzyme thrombin,[4] and 4-phenylpipecolic acid is a component of selective trypsin inhibitor MNAPPA (Fig. 1).[5] In the general preparation of the pipecolic acid skeleton, the common synthetic methods include intramolecular cyclization[6] or a ring-closing metathesis reaction of diallylamine.[7]

In preliminary studies,[8] reactions were investigated regarding the structural framework of 4-substituted-1,2,5,6-tetrahydropyridine **1** that occurred during the preparation of other frameworks, including benzonaphthyridine,[8a] 3-aryl-3-formylpyrrolidine,[8b,c] β-aminoarylketone,[8d] benzo[*f*]isoquinoline,[8e] 4-aryl-3-fluoropiperidine,[8f] and others, as shown in Figure 2. Given the synthetic advantages of this initial material, a strategy was developed for the synthesis of 1,2,4-trisubstituted- or 1,2,3,4-tetrasubstituted-1,2,5,6-tetrahydropyridines. An easy three-step synthetic transformation of 4-aryl-2-cyano-1-sulfonyl-1,2,5,6-tetrahydropyridines **2** or 2-allyl-4-aryl-1-sulfonyl-1,2,5,6-tetrahydropyridines **3** from 4-aryl-1,2,5,6-tetrahydropyridines **1** involves: (1) bromomethoxylation of skeleton **1** with NBS in methanol; (2) dehydrobromination of 4-aryl-3-bromo-4-methyoxy-1,2,5,6-tetrahydropyridines **4** with DBU in tetrahydrofuran; and (3) a BF_3-OEt_2-promoted reaction of the corresponding enamine with trimethylsilyl-based nucleophiles.

2. Results and discussion

For the NBS-mediated bromomethoxylation of 4-aryl-1,2,5,6-tetrahydropyridine **1**, olefin **1a** was initially chosen as the model substrate, as shown in Table 1 and Scheme 1. Treatment of compound **1a** with NBS in methanol produced *trans*-1,2-methoxybromide **4a**. Then, some commercial tertiary amines were examined in the dehydrobromination under a number of conditions, such as prolonged reaction time, elevated temperature, and different solvents. When the treatment of compound **4a** involved aromatic

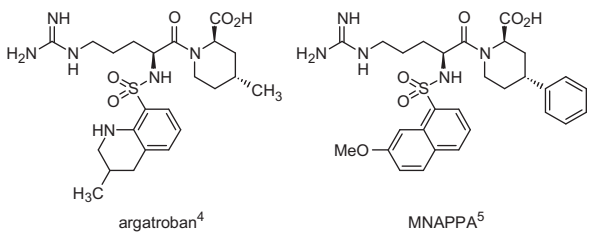

Figure 1. Structures of argatroban and MNAPPA.

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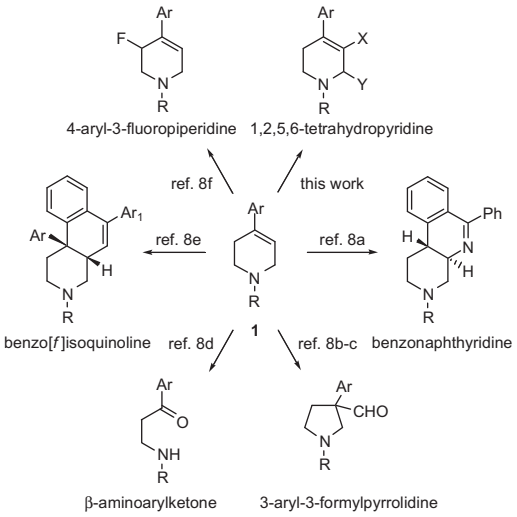
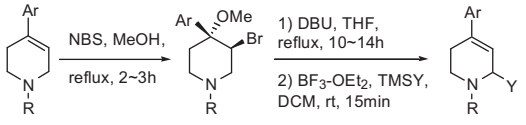


Figure 2. Synthetic approaches to 4-Substituted-1,2,5,6-tetrahydropyridine.

Table 1
Synthesis of compounds **2**, **3**, and **4**[a,b]



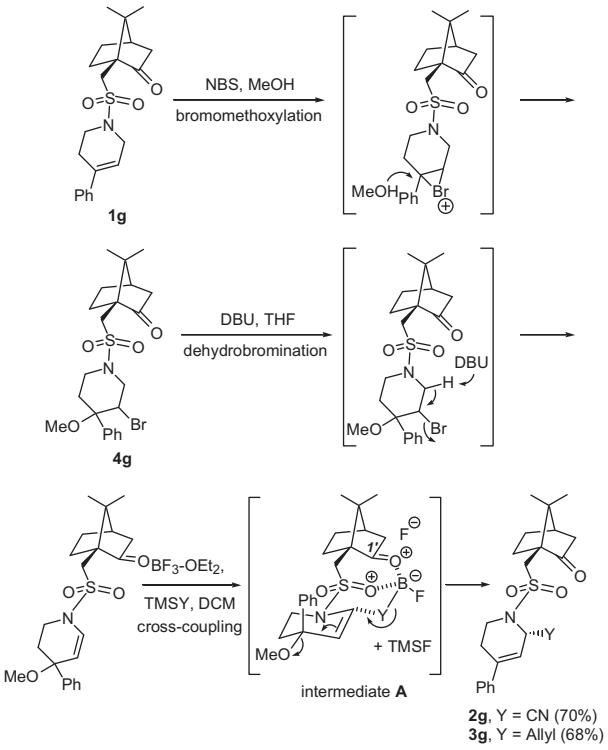
Entry	**1** (Ar, R)	**4**, Yield	**2**, Yield	**3**, Yield
1	**1a**, Ph, Bs	**4a**, 72%	**2a**, 72%	**3a**, 74%
2	**1b**, 4-FPh, Bs	**4b**, 63%	**2b**, 78%	**3b**, 70%
3	**1c**, 3-CF_3Ph, Bs	**4c**, 51%	**2c**, 70%	**3c**, 72%
4	**1d** 3-CF_3–4ClPh, Bs	**4d**, 50%	**2d**, 72%	**3d**, 69%
5	**1e**, Ph, Bz	**4e**, 69%	**2e**, 60%	**3e**, 61%
6	**1f**, Ph, 4-MeOPhCO	**4f**, 62%	**2f**, 65%	**3f**, 61%
7	**1g**, Ph, (1*S*)-SO_2Camphor	**4g**, 60%	**2g**, 70%	**3g**, 68%

[a] For the best reaction conditions: (1) olefins **1** (1.0 equiv), NBS (1.1 equiv), MeOH (10 mL), reflux, 2–3 h, (2) methoxybromides **4** (1.0 equiv), DBU (10.0 equiv), THF (10 mL), reflux, 10–14 h, (3) the resulting enamine, BF_3-OEt_2 (1 mL), TMSY (1 mL), DCM (10 mL), RT, 15 min.

[b] The isolated products were >95% pure as determined by ^{1}H NMR analysis.

amine (4-dimethylaminopyridine or pyridine) in tetrahydrofuran at reflux, 4-phenylpyridine was isolated as the major product among the product mixture. For the treatment of compound **4a** with aliphatic amine (1,4-diazabicyclo[2.2.0]octane, diisopropylethylemine or triethylamine) in tetrahydrofuran or dichloromethane at reflux, the starting material was recovered as the major product. During the experimental dehydrobromination process, when the treatment of compound **4a** produced an excess amount of amidine base (DBU) in tetrahydrofuran (at reflux for 10 h), the corresponding 4-methoxy-4-phenyl-1,2,3,4-tetrahydropyridine with enamino functional group produced a high yield.[9] Noticeably, this enamine was unstable.

Next, 2-cyano-4-phenyl-1,2,5,6-tetrahydropyridine **2a** resulted in a sole isomer through the coupling reaction of the enamine with BF_3-OEt_2 in the co-solvent of trimethylsilyl cyanide (3 mL) and dichloromethane (10 mL) at rt for 15 min.[9] Attempts to perform the reaction with the other trimethylsilyl-based nucleophiles (i.e., the vinyl, phenyl, and 2-thienyl group) failed. The total synthetic procedure was monitored through a thin layer chromatography until the reaction was complete. This study showed a concise and efficient synthetic approach to construct **2a** from **4a** with 72%



Scheme 1. The three-step reaction mechanisms from compound **1g** to compound **2g** or **3g**.

yield from the overall two-step protocol. With the above results in mind, treatment of olefins **1a**–**g** produced methoxybromides **4a**–**g** with 50–72% yields. Then, cyanides **2a**–**g** were yielded with 60–78% overall yields using the two-step protocol. The structural framework of compound **2g** was determined using single-crystal X-ray analysis (Diagram 1).[10] After changing the trimethylsilyl-based nucleophile from cyano group to allyl group, 2-allyl-4-aryl-1,2,5,6-tetrahydropyridines **3a**–**g** were also isolated in 61–74% yields by the above protocols. In particular, (1′*S*,2*S*)-**2g** and (1′*S*,2*R*)-**3g** were isolated with a 70% yield (96% de) and a 68% yield

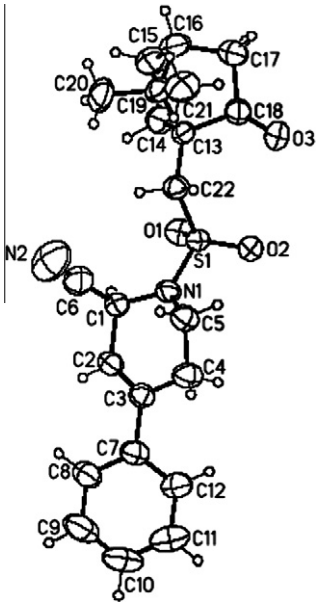


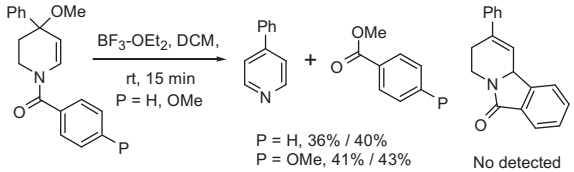
Diagram 1. X-ray structure of compound **2g**.

(95% de) from olefin **4g**, shown in entry 7. During the purification process, the other isomer was not isolated under this condition. It has been confirmed that the most likely explanation (see Scheme 1) was that the chelated boron intermediate **A** between the 1′-carbonyl and sulfonyl group generated the chair-like conformation affecting the enatioselective introduction of the trimethylsilyl-based nucleophiles at the 2-position of piperidine ring system. Our typical experimental procedure suggested a general and efficient alternative to the preparation of chiral 2-substitued 4-phenyl-1,2,5,6-tetrahydropyridines via the chiral camphorsulfone auxiliary.

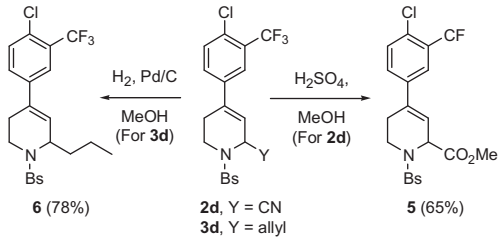
But, when BF_3-OEt_2-promoted coupling reaction of the enamine group was treated without the addition of trimethylsilyl-based nucleophiles (Equation 1), methyl 4-methoxybenzoate or benzoate, and 4-phenylpyridine were isolated. The expected tricyclic ring framework of pyridoisoindolone was not observed during the process.

To further explore the application of skeletons **2** and **3**, compounds **2d** and **3d** were chosen as a model substrate to synthesize methyl pipecolinate[6,7] and coniine[11] with 4-aryl substitutent, as shown in Scheme 2. Under acidic hydrolysis, ester **5** was obtained through the treatment of cyanide **2d** with sulphuric acid in methanol in65% yield. Hydrogenation of olefin **3d** with hydrogen in the presence of palladium produced 78% yield of compound **6**. It presented a new method for preparing methyl 4-arylpipecolate and 4-arylconiine derivatives.

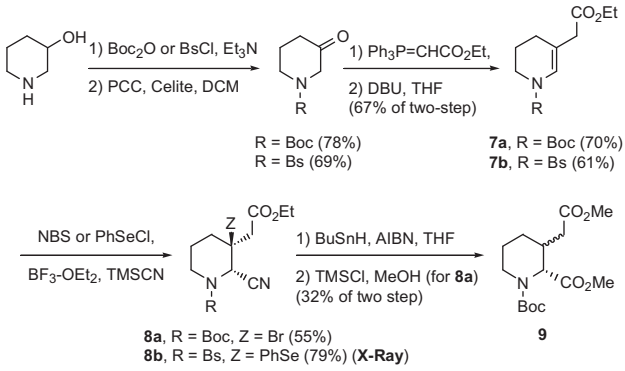
On the basis of the above mentioned two-step protocol, methyl 3-pipecolinoglutamate was chosen as the next target.[12] Precursor **7** was provided from 3-hydroxypiperidine via N-protection, PCC-oxidation, Wittig olefination, and DBU-mediated deconjugation (Scheme 3).[13] The overall yields of compounds **7a** and **7b** were about 55% and 42%, respectively, from the 3-hydroxypiperidine. BF_3-OEt_2-promoted, intermolecular reaction of the enamine **7a** and **7b** with NBS or PhSeCl in the presence of trimethylsilyl cyanide was further transformed into tertiary bromide **8a** or phenylselenide **8b** with 55% or 79% yield. Finally, diester **9** was produced by the debromination of compound **8a** and hydrolysis of the resulting cyanoester with a 32% two-step yield.[14] Interestingly, the treatment of compound **8b** in the above reaction conditions resulted in compound **7b** via reductive decyanation.[15] Notably, this strategy was a reversible process between compounds **7b** and **8b**.



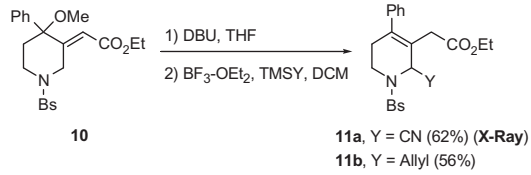
Equation 1. BF_3-OEt_2-mediated reaction of enamines.



Scheme 2. Synthesis of compounds **5** and **6**.



Scheme 3. Synthesis of compound **9**.



Scheme 4. Synthesis of phenylhomokainoid **11a**.

Furthermore, treatment of compound **10** using the two-step protocol converted it into 1,2,3,4-tetrasubstituted-1,2,5,6-tetrahydropyridine **11a** and **11b**, as shown in Scheme 4. Compound **10** was previously synthesized by selenium dioxide-mediated *trans*-methoxyhydroxylation of olefin **1** and was subsequently followed by Jones oxidation and Wittig olefination.[16] Skeleton **11** was similar to homokainoid.[12] The two structures of phenylselenide **8b** and cyanoester **11a** were determined using single-crystal X-ray analysis.[17]

3. Conclusion

A synthetic methodology for producing a series of 1,2,4-trisubstituted- or 1,2,3,4-tetrasubstituted-4-aryl-1,2,5,6-tetrahydropyridines has been successfully presented using NBS-mediated allylic bromination, dehydrobromination with DBU, and BF_3-OEt_2-promoted cross coupling involving trimethylsilyl-based nucleophiles. Under the two-step protocol, homokainoids **9** and **11a** were also synthesized. Several structures of the target products were confirmed by X-ray crystal analysis. Further studies on the biological evaluation of the desulfonated homokainoids are actively underway in laboratories.

Acknowledgments

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9. A representative two-step synthetic transformation of skeleton **2** or **3** from olefin **1** is as follows: NBS (200 mg, 1.1 mmol) was added to a solution of olefin **1** (1.0 mmol) in methanol (10 mL) at reflux temperature. The reaction mixture was stirred at reflux for 2–3 h. Saturated sodium bicarbonate solution (2 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product. Purification on silica gel (hexane/AcOEt = 6/1–2/1) afforded skeleton **4**. *Representative data for compound* **4a**: mp = 128–129 °C; HRMS (ESI, M^++1) calcd for $C_{18}H_{21}BrNO_3S$ 410.0426, found 410.0428; ^{1}H NMR (400 MHz): δ 7.85–7.82 (m, 2H), 7.64–7.54 (m, 3H), 7.40–7.29 (m, 5H), 4.20 (dd, J = 2.0, 4.4 Hz, 1H), 3.93 (dt, J = 2.0, 12.8 Hz, 1H), 3.85–3.81 (m, 1H), 3.48 (dd, J = 2.0, 12.8 Hz, 1H), 2.83 (s, 3H), 2.77 (dd, J = 4.4, 14.0 Hz, 1H), 2.70 (dt, J = 2.0, 12.8 Hz, 1H), 2.13 (ddd, J = 2.0, 4.4, 14.0 Hz, 1H); ^{13}C NMR (100 MHz): δ 140.55, 137.13, 132.80, 129.08 (2×), 128.35 (2×), 128.30, 127.53 (2×), 126.48 (2×), 77.18, 53.98, 50.85, 48.78, 41.16, 23.62; anal. calcd for $C_{18}H_{20}BrNO_3S$: C, 52.69; H, 4.91; N, 3.41. Found: C, 52.91; H, 4.83; N, 3.62. DBU (1.5 g, 10.0 mmol) was added to a solution of **4** (0.8 mmol) in tetrahydrofuran (10 mL) at reflux temperature. The reaction mixture was stirred at reflux for 10–14 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product. Without further purification, a solution of boron trifluoride etherate (~4.0 mmol, 0.5 mL) in dichloromethane (5 mL) was added to a stirred solution of the resulting enamine product in trimethylsilyl cyanide (3 mL) or allyltrimethylsilane (3 mL) in dichloromethane (10 mL) at rt. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 6/1–3/1) afforded skeleton **2** or **3**. *Representative data for compound* **2a**: mp = 149–150 °C; HRMS (ESI, M^++1) calcd for $C_{18}H_{17}N_2O_2S$ 325.1011, found 325.1012; ^{1}H NMR (400 MHz): δ 7.94–7.91 (m, 2H), 7.68–7.56 (m, 3H), 7.39–7.30 (m, 5H), 5.97 (ddd, J = 1.2, 2.4, 5.2 Hz, 1H), 5.41 (ddd, J = 1.2, 2.4, 3.6 Hz, 1H), 4.12 (ddt, J = 1.2, 6.4, 13.2 Hz, 1H), 3.13 (ddd, J = 4.0, 13.2, 17.2 Hz, 1H), 2.84–2.74 (m, 1H), 2.52 (ddd, J = 0.8, 2.4, 17.2 Hz, 1H); ^{13}C NMR (100 MHz): δ 140.34, 138.56, 137.49, 133.67, 129.33 (2×), 128.76, 128.68 (2×), 127.61 (2×), 125.34 (2×), 114.88, 114.76, 44.62, 40.19, 27.32; anal. calcd for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.89; H, 5.21; N, 8.79. *Representative data for compound* **3a**: Gum; HRMS (ESI, M^++1) calcd for $C_{20}H_{22}NO_2S$ 340.1371, found 340.1372; ^{1}H NMR (400 MHz): δ 7.87–7.83 (m, 2H), 7.54–7.42 (m, 3H), 7.30–7.21 (m, 3H), 7.16–7.14 (m, 2H), 5.99–5.97 (m, 1H), 5.94–5.83 (m, 1H), 5.14–5.08 (m, 2H), 4.62–4.58 (m, 1H), 4.04–3.98 (m, 1H), 3.29 (ddd, J = 6.0, 10.0, 14.4 Hz, 1H), 2.52–2.44 (m, 2H), 2.18–2.12 (m, 2H); ^{13}C NMR (100 MHz): δ 141.33, 140.39, 135.81, 134.11, 132.45, 128.99 (2×), 128.38 (2×), 127.53, 126.92 (2×), 125.05 (2×), 123.71, 117.99, 53.83, 40.02, 39.01, 25.37.
10. CCDC 776258 (**2a**) and 783909 (**2g**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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17. CCDC 789417 (**8b**) and 783908 (**11a**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).